REMARKS

Claims 1, 2, 4, 5, 7-16, 18, 19, and 21-28 were pending in the application. Claim 12 has been cancelled as being drawn to a non-elected invention. Claims 1, 2, 4, 5, 7-11, 13-16, 18, 19, 21-28 have been amended. The claims have been amended at the request of the Examiner to specify a non-human animal. Thus, upon entry of this Amendment, claims 1, 2, 4, 5, 7-11, 13-16, 18, 19, 21-28 are pending in the application.

No new matter has been added. Applicants request that the amendments to the specification and claims be entered. The foregoing claim amendments and cancellation should in no way be construed as an acquiescence to any of the Examiner's rejections and were made solely to expedite prosecution of the present application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Response to Restriction Requirement

The Examiner has required restriction to one of the following inventions under 35 U.S.C. 121:

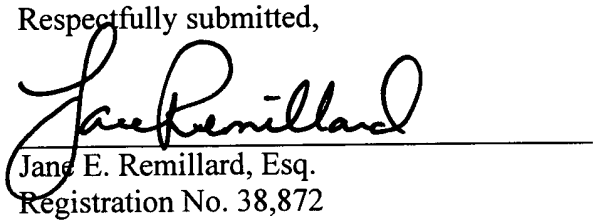
I. Claims 1, 2, 4, 5, 7-11, 13-16, 18, 19, 21-28, drawn to a non-human transgenic animal comprising a polynucleotide encoding a fusion protein that inhibits transcription in a eukaryotic cell.

II. Claims 1, 2, 4, 5, 7-12, 14-16, 18, 19, 21-28, drawn to a transgenic plant comprising a polynucleotide encoding a fusion protein that inhibits transcription in a eukaryotic cell.

Applicants hereby elect the Group I invention (claims 1, 2, 4, 5, 7-11, 13,-16, 18, 19, 21-28) for prosecution, without traverse.

If a telephone conversation with Applicants' attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' attorney at (617) 227-7400.

Respectfully submitted,



Jane E. Remillard, Esq.
Registration No. 38,872
Attorney for Applicants

LAHIVE & COCKFIELD, LLP
28 State Street
Boston, MA 02109
Tel. (617) 227-7400
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. **(Amended)** A non-human transgenic animal ~~organism~~ having a transgene comprising a polynucleotide sequence encoding a fusion protein which inhibits transcription in eukaryotic cells, the fusion protein comprising a first polypeptide which is a Tet repressor or mutated Tet repressor that binds to a *tet* operator sequence, operatively linked to a heterologous second polypeptide which inhibits transcription in eukaryotic cells.

2. **(Amended)** The animal ~~organism~~ of claim 1, wherein the first polypeptide of the fusion protein is a Tet repressor that binds to *tet* operator sequences in the absence but not the presence of tetracycline or a tetracycline analogue.

4. **(Amended)** The animal ~~organism~~ of claim 2, wherein the first polypeptide comprises an amino acid sequence shown in SEQ ID NO: 17.

5. The animal ~~organism~~ of claim 1, wherein the first polypeptide of the fusion protein is a mutated Tet repressor that binds to *tet* operator sequences in the presence but not the absence of tetracycline or a tetracycline analogue.

7. The animal ~~organism~~ of claim 5, wherein the mutated Tet repressor has at least one amino acid substitution compared to a wild-type Tet repressor.

8. The animal ~~organism~~ of claim 7, wherein the mutated Tet repressor has an amino acid substitution at least one amino acid position corresponding to an amino acid position selected from the group consisting of position 71, position 95, position 101 and position 102 of a wild-type Tn10-derived Tet repressor amino acid sequence.

9. The animal ~~organism~~ of claim 8, wherein the mutated Tet repressor comprises an amino acid sequence shown in SEQ ID NO: 19.

10. The animal ~~organism~~ of claim 1, wherein the second polypeptide comprises a transcription silencer domain of a protein selected from the group consisting of v-erbA, the Drosophila Krueppel protein, the retinoic acid receptor alpha, the thyroid hormone

receptor alpha, the yeast Ssn6/Tup1 protein complex, the Drosophila protein even-skipped, SIR1, NeP1, the Drosophila dorsal protein, TSF3, SFI, the Drosophila hunchback protein, the Drosophila knirps protein, WT1, Oct-2.1, the Drosophila engrailed protein, E4BP4 and ZF5.

11. The animal ~~organism~~ of claim 1, further having a second transgene comprising a gene of interest operably linked to at least one *tet* operator sequence.

13. The animal ~~organism~~ of claim 1, which is selected from a group consisting of a cow, a goat, a sheep and a pig.

14. A method for modulating transcription of the second transgene in the transgenic animal ~~organism~~ of claim 11, comprising administering tetracycline or a tetracycline analogue to the animal ~~organism~~.

15. A non-human transgenic animal ~~organism~~ having a transgene comprising a polynucleotide sequence encoding a fusion protein which inhibits transcription in eukaryotic cells, the fusion protein comprising a first polypeptide which is a Tet repressor or a mutated Tet repressor that binds to a *tet* operator sequence, operatively linked to a heterologous second polypeptide which inhibits transcription in eukaryotic cells, wherein the transgene is integrated by at a predetermined location within a chromosome within cells of the animal ~~organism~~.

16. The animal ~~organism~~ of claim 15, wherein the first polypeptide of the fusion protein is a Tet repressor that binds to *tet* operator sequences in the absence but not the presence of tetracycline or a tetracycline analogue.

18. The animal ~~organism~~ of claim 16, wherein the first polypeptide comprises an amino acid sequence shown in SEQ ID NO: 17.

19. The animal ~~organism~~ of claim 16, wherein the first polypeptide of the fusion protein is a mutated Tet repressor that binds to *tet* operator sequences in the presence but not the absence of tetracycline or a tetracycline analogue.

21. The animal ~~organism~~ of claim 19, wherein the mutated Tet repressor has at least one amino acid substitution compared to a wild-type Tet repressor.

22. The animal ~~organism~~ of claim 21, wherein the mutated Tet repressor has an amino acid substitution at least one amino acid position corresponding to an amino acid position selected from the group consisting of position 71, position 95, position 101 and position 102 of a wild-type Tn10-derived Tet repressor amino acid sequence.

23. The animal ~~organism~~ of claim 22, wherein the mutated Tet repressor comprises an amino acid sequence shown in SEQ ID NO: 19.

24. The animal ~~organism~~ of claim 15, wherein the second polypeptide comprises a transcription silencer domain of a protein selected from the group consisting of v-erbA, the Drosophila Krueppel protein, the retinoic acid receptor alpha, the thyroid hormone receptor alpha, the yeast Ssn6/Tup1 protein complex, the Drosophila protein even-skipped, SIR1, NeP1, the Drosophila dorsal protein, TSF3, SFI, the Drosophila hunchback protein, the Drosophila knirps protein, WT1, Oct-2.1, the Drosophila engrailed protein, E4BP4 and ZF5.

25. The animal ~~organism~~ of claim 15, further having a second transgene comprising a gene of interest operably linked to at least one *tet* operator sequence.

26. A method for modulating transcription of the second transgene in the transgenic animal ~~organism~~ of claim 25, comprising administering tetracycline or a tetracycline analogue to the animal ~~organism~~.

27. A non-human transgenic animal ~~organism~~ having a transgene integrated into the genome of the animal ~~organism~~ and also having a *tet* operator-linked gene in the genome of the animal ~~organism~~, wherein:

the transgene comprises a transcriptional regulatory element functional in cells of the animal ~~organism~~ operatively linked to a polynucleotide sequence encoding a fusion protein which inhibits transcription of said *tet* operator linked gene,

said fusion protein comprises a first polypeptide that is a Tet repressor operably linked to a heterologous second polypeptide which inhibits transcription of said *tet* operator-linked gene in eucaryotic cells,

said *tet* operator-linked gene confers a detectable and functional phenotype on the ~~organism~~ animal when expressed in cells of the animal ~~organism~~,

said transgene is expressed in cells of the animal ~~organism~~ at a level sufficient to produce amounts of said fusion protein that are sufficient to inhibit transcription of the *tet* operator-linked gene; and

in the absence of tetracycline or a tetracycline analogue in the animal ~~organism~~, said fusion protein binds to the *tet* operator-linked gene and inhibits transcription of the *tet* operator linked gene, wherein the level of expression of the *tet* operator-linked gene can be upregulated by administering tetracycline or a tetracycline analogue to the animal ~~organism~~.

28. A non-human transgenic animal ~~organism~~ having a transgene integrated into the genome of the animal ~~organism~~ and also having a *tet* operator-linked gene in the genome of the animal ~~organism,~~ wherein:

the transgene comprises a transcriptional regulatory element functional in cells of the animal ~~organism~~ operatively linked to a polynucleotide sequence encoding a fusion protein which inhibits transcription of said *tet* operator linked gene,

said fusion protein comprises a first polypeptide that is a mutated Tet repressor that binds to *tet* operator sequences in the presence, but not the absence, of tetracycline or a tetracycline analogue, operably linked to a heterologous second polypeptide which inhibits transcription of said *tet* operator-linked gene in eucaryotic cells,

said *tet* operator-linked gene confers a detectable and functional phenotype on the animal ~~organism~~ when expressed in cells of the animal ~~organism~~,

said transgene is expressed in cells of the animal ~~organism~~ at a level sufficient to produce amounts of said fusion protein that are sufficient to inhibit transcription of the *tet* operator-linked gene; and

in the presence of tetracycline or a tetracycline analogue in the animal ~~organism~~, said fusion protein binds to the *tet* operator-linked gene and inhibits transcription of the *tet* operator linked gene, wherein the level of expression of the *tet* operator-linked gene can be upregulated by depleting tetracycline or a tetracycline analogue from the animal ~~organism~~.